STRATEGIC PROPOSALS FOR PREDICTING DRUG-DRUG INTERACTIONS DURING NEW DRUG DEVELOPMENT: BASED ON SIXTEEN DEATHS CAUSED BY INTERACTIONS OF THE NEW ANTIVIRAL SORIVUDINE WITH 5-FLUOROURACIL PRODRUGS

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In 1993, sixteen Japanese patients died from drug interactions of oral 5-fluorouracil (5-FU) prodrugs with the new oral antiviral drug, sorivudine (SRV), for herpes zoster within 40 days after SRV was approved by the Japanese government and began to be clinically used. All the patients were receiving one of 5-FU prodrugs daily for long-term anti-cancer chemotherapy when SRV was administered to them by the schedule of daily treatment for 7 days. Within several days after the SRV administration, these patients showed severe symptoms of toxicity, including diarrhea with bloody flux and marked decreases in white blood cell and platelet counts.

Our toxicokinetic, enzymatic, histochcmical, and hematological studies using rats strongly suggested that these deaths were attributable to the interaction of 5-FU formed from the anti-cancer prodrug and (E)-5-(2-bromovinyl)uracil (BVU) from SRV. BVU was generated from SRV by gut flora as previously reported (1), absorbed from the intestinal membrane, irreversibly inactivated hepatic dihydropyrimidine dehydrogenase (DPD) as a suicide inhibitor, and markedly enhanced the 5-FU levels in plasma and tissues, including bone marrow and intestines. DPD is a soluble homo-dimeric protein of molecular mass of 204-216 kDa with FMN/FAD and an Fe/S cluster in each subunit, exists in most part in the liver of various mammals, and plays an important role in determining the tissue levels of the anti-cancer drug, 5-FU, and the endogenous pyrimidines, uracil and thymine. 5-FU is dihydrogenated at the 5,6-double bond of the pyrimidine ring by DPD in the presence of NADPH and then rapidly, enzymatically hydrolyzed to α-fluoro-β-alanine. DPD purified from rat liver cytosol was rapidly inactivated in the presence of NADPH by covalent binding with [14C]BVU. However, SRV showed no inhibitory effect on DPD. All rats repeatedly given SRV and the 5-FU prodrug, tegafur (FT), once daily died within 10 days, whereas the animals given the same dose of SRV or FT alone showed no symptom of toxicity for a period more than 20 days. The 5-FU levels in plasma, intestines, and bone marrow of the animals extremely increased by the simultaneous administration of SRV (30 mg/kg/day) and FT (60 mg/kg/day), e.g. Cmax (μg/ml or g) and AUC (μg/ml or g x hr) were 2.6 and 18.6 for plasma, 3.3 and 56.5 for intestines and 2.8 and 39.7 for bone marrow, respectively, on day 4 when most of these animals showed diarrhea with bloody flux. In contrast to these animals, rats repeatedly given the same dose of FT alone showed Cmax (μg/ml or g) and AUC (μg/ml or g x hr) of 5-FU on day 4: 0.2 and 2.3 for plasma, 0.2 and 4.2
for intestines, respectively, and undetectable levels for bone marrow. Bone marrow cells in animals given SRV and FT showed a marked decrease in colony formation of granulocytes and macrophages; e.g. colony-forming activity decreased to 2.4% that of controls by day 2, and their white blood cell and platelet counts also decreased to 17.6 and 25.7% of controls, respectively, by day 6 when one third of the animals died. There were marked atrophy of intestinal membrane mucosa and severe anorexia by day 4 in the animals given SRV and FT.

We have very recently obtained direct evidence for the covalent binding of [14C]BVU to human DPD in the presence of NADPH, leading to a complete loss of enzyme activity.

The sixteen deaths would have been avoided if the following previous demonstration had been more carefully considered in the safety/risk assessment of drug interactions during the development of the new antiviral SRV: 1) BVU is generated from a part of orally administered SRV by gut flora in rats and absorbed from intestines (1), 2) simultaneous i.p. administration of 5-FU and BVU increases the plasma level of the anti-carcinogenic agent in rats (2), and 3) BVU is likely to inhibit rat liver DPD irreversibly in the presence of NADPH in vitro (2).

A careful study should be made on the safety/risk assessment of the drug interactions between a new drug during development and known drugs, such as anti-cancer chemotherapeutic agents with narrow therapeutic range and those affecting cardiovascular, respiratory, and central nervous systems, because the elevated tissue levels of these drugs may often result in severe toxicity. Strategic proposals for predicting drug interactions during the development of a new drug and avoiding the severe toxicity after marketing:

1) Identify the pharmacologically active form of the new drug. In case of SRV, its antiviral activity is exerted by SRV but not by the metabolite BVU. However, BVU is a pharmacologically (toxicologically) active form in view of leading to the marked increase in the tissue levels of 5-FU which is also a pharmacologically active form from FT and other 5-FU prodrugs.

2) Identify the enzyme or its isoform primarily involved in determining the plasma and tissue levels of the pharmacologically active form of the new and known drugs expected to be frequently, simultaneously administered. In case of SRV, many of the patients receiving 5-FU or its prodrug could be expected to have herpes zoster as a result of immuno-deficiency attributable to the bone marrow damage by 5-FU. Hepatic DPD activity should have to be determined after administration of SRV and BVU to rats. DPD isolated from rat liver could be useful for predicting the lethal interaction between 5-FU and BVU in humans because DPD had been known to occur in single form and to determine the tissue 5-FU levels as the sole enzyme in the human as well as in the rats.

3) Estimate the plasma levels of active forms of simultaneously administered drugs with toxicological importance during clinical trials. In case of SRV, two subjects receiving a 5-FU prodrug were pointed out later to die by administration of SRV during phase II clinical trial. However, no blood samples was taken from these subjects to determine the plasma 5-FU level.

References
